CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 064171

Trade Name: PAROMOMYCIN SULFATE CAPSULE USP 250MG (BASE)

Generic Name: Paromomycin Sulfate Capsule USP 250mg (base)

Sponsor : Caraco Pharmaceutical Laboratories, Ltd.

Approval Date: June 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 064171

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 064171

APPROVAL LETTER

AADA 64-171

JUN 30 1997

Caraco Pharmaceutical Laboratories, Ltd.
Attention: Annie Holt
1150 Elijah McCoy Drive
Detroit, MI 48202

Dear Madam:

This is in reference to your abbreviated antibiotic drug application dated December 29, 1995, submitted pursuant to Section 507 of the Food, Drug, and Cosmetic Act, for Paromomycin Sulfate Capsules USP, 250 mg (base),

Reference is also made to your amendments dated May 30 and December 10 1996; April 18, June 13 and June 19, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Paromomycin Sulfate Capsules, USP, 250 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Humatin Capsules® 250 mg (base) of Parke Davis, Division of Warner Lambert Company). Your disintegration testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 6/30/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064171

FINAL PRINTED LABELING

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

*Each capsule, for oral administration, contains paromomycin sulfate equivalent to 250 mg paromomycin.

Each capsule also contains the following inactive ingredients: FD&C Green #3, FD&C Yellow #5 (tartrazine), gelatin, and titanium dioxide.

ISS 3/97

NDC 57664-175-08

Paromomycin Sulfate

Capsules, USP

250 mg*

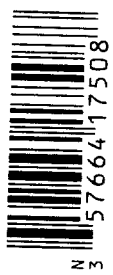
100 Capsules

CAUTION: Federal law prohibits dispensing without prescription.

CARACO PHARMACEUTICAL LABORATORIES, LTD. DETROIT, MI 48202

USUAL DOSAGE:
See package outsert for complete prescribing information.

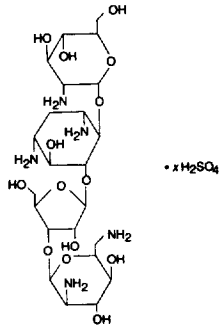
Keep this and all drugs out of the reach of children.



Paromomycin Sulfate
Capsules, USP

DESCRIPTION

Paromomycin sulfate is a broad spectrum antibiotic produced by *Streptomyces riomosus* var. *paromomycinus*. It is a white, amorphous, stable, water-soluble product. Paromomycin sulfate is designated chemically as *O*-2,6-Diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-*O*-β-D-ribofuranosyl-(1→5)-*O*-[2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)]-2-deoxystreptamine sulfate (salt). The molecular formula is $C_{23}H_{45}N_5O_{14} \cdot xH_2SO_4$, with a molecular weight of 615.64 (base). Its structural formula is:



Each capsule, for oral administration, contains paromomycin sulfate equivalent to 250 mg paromomycin. Each capsule also contains the following inactive ingredients: FD&C Green #3; FD&C Yellow #5 (tartrazine); gelatin, NF; and titanium dioxide, USP.

CLINICAL PHARMACOLOGY

The *in vitro* and *in vivo* antibacterial action of paromomycin closely parallels that of neomycin. It is poorly absorbed after oral administration, with almost 100% of the drug recoverable in the stool.

INDICATIONS AND USAGE

Paromomycin sulfate is indicated for intestinal amebiasis—acute and chronic (NOTE—It is not effective in extraintestinal amebiasis); management of hepatic coma—as adjunctive therapy.

CONTRAINDICATIONS

Paromomycin sulfate is contraindicated in individuals with a history of previous hypersensitivity reactions to it. It is also contraindicated in intestinal obstruction.

PRECAUTIONS

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. Constant observation of the patient is essential. If new infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

The drug should be used with caution in individuals with ulcerative lesions of the bowel to avoid renal toxicity through inadvertent absorption.

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Nausea, abdominal cramps, and diarrhea have been reported in patients on doses over 3 g daily.

DOSAGE AND ADMINISTRATION

Intestinal amebiasis: Adults and Children: Usual dose—25 to 35 mg/kg body weight daily, administered in three doses with meals, for five to ten days.

Management of hepatic coma: Adults: Usual dose—4 g daily in divided doses, given at regular intervals for five to six days.

HOW SUPPLIED

Paromomycin Sulfate Capsules, each contain paromomycin sulfate equivalent to 250 mg paromomycin. The capsule is green/yellow, imprinted "175" in black ink on the cap and body.

NDC 57664-175-08: Bottles of 100

Store at controlled room temperature 15°-30°C (59°-86°F).

Protect from moisture.

Caution—Federal law prohibits dispensing without prescription.

C.S. No. 5106T01
ISS. 3/97

CARACO
PHARMACEUTICAL
LABORATORIES, LTD.
DETROIT, MI 48202

5106T01

PAROMOMYCIN SULFATE Capsules, USP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064171

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. AADA # 64-171

3. NAME AND ADDRESS OF APPLICANT

Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, Michigan 48202

4. BASIS OF SUBMISSION
Humatin Capsules
by Parke-Davis

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Paromomycin Sulfate
Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Date of Application: December 29, 1995
Date of Receipt: January 2, 1996
Major Amendment dated December 10, 1996
Facsimile Amendment dated: April 18, 1997

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsules

14. POTENCY
250 mg

15. CHEMICAL NAME AND STRUCTURE

$C_{23}H_{45}N_5O_{14} \cdot H_2SO_4$

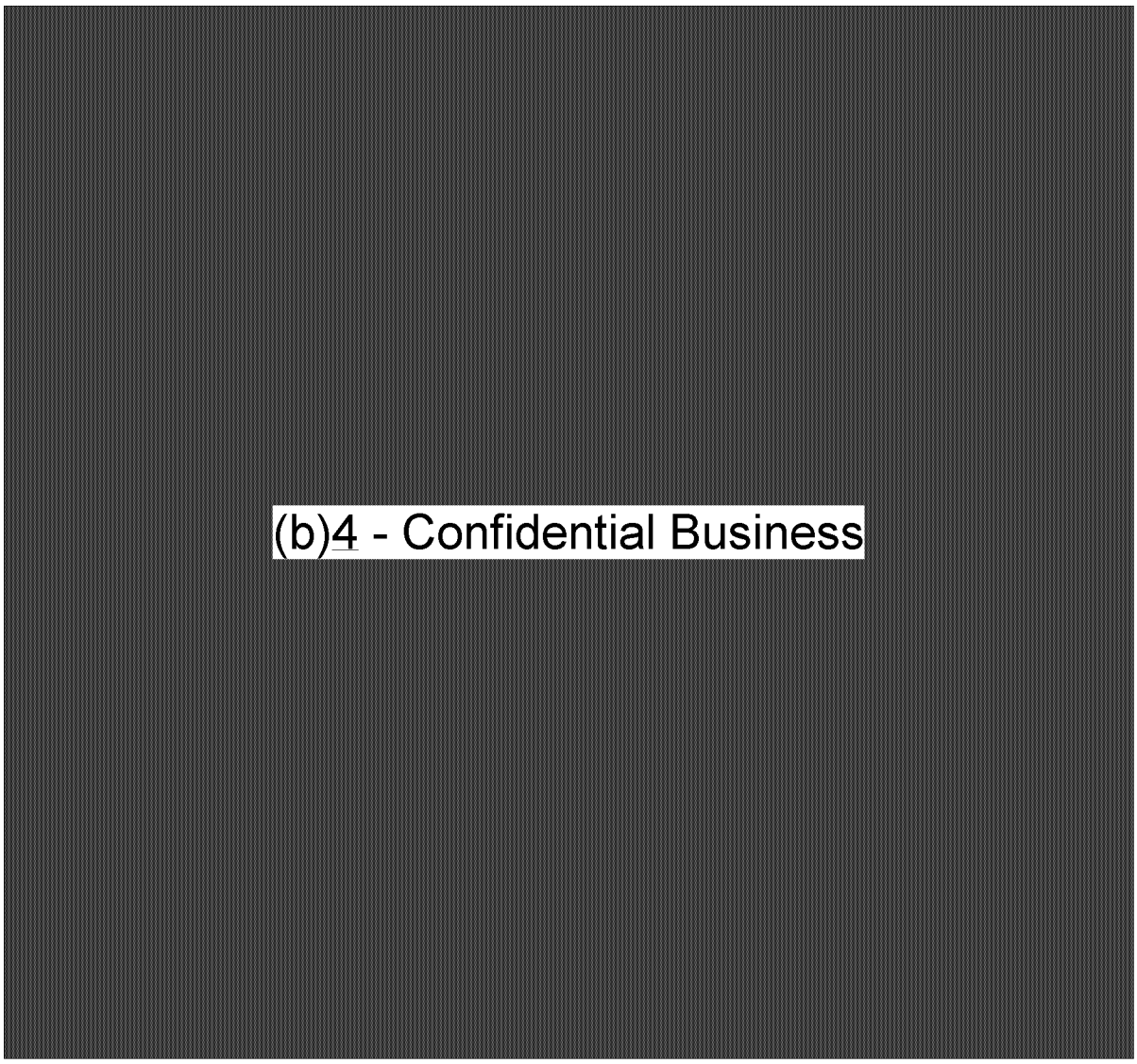
Paromomycin Sulfate is the sulfate salt of an antibiotic substance or substances produced by the growth of *Streptomyces rimosus* var. *paromomycinus*, or a mixture of two or more such salts.

Paromomycin sulfate is indicated for intestinal amebiasis - acute and chronic; management of hepatic coma - as adjunctive therapy.

16. RECORDS AND REPORTS
N/A

17. COMMENTS

This is a review of the Facsimile Amendment dated April 18, 1997, which is in response to our Facsimile deficiency dated March 27, 1997.



Reviewer's comment

The applicant's commitment is satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application may be approved with an acceptable EER for Caraco and the other firms listed under item 24.

19. REVIEWER: V.Walton

DATE COMPLETED: April 25, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064171

BIOEQUIVALENCE REVIEW(S)

JUN 20 1996

Paromomycin Sulfate
Capsules, 250 mg, USP
ANDA 64-171
Reviewer: Man M. Kochhar

Caraco Pharmaceutical
Detroit, Michigan
Submission Date:
December 29, 1995

Review of a Waiver Request

Introduction

Paromomycin is a aminoglycoside antibiotic, isolated from cultures of Streptomyces rimosus, is amebicidal both in vitro and in vivo. Paromomycin acts directly on amoebae but also has antibacterial activity against normal and pathogenic microorganisms in the gastrointestinal tract. It is supplied in capsules, each containing 250 mg. After oral administration, little of the drug is absorbed into the systemic circulation. The main side effect of this antibiotic is gastrointestinal upset and diarrhea.

Comment:

1. The formulation of the test product and innovator product Humatin 250 mg capsule (Parke-Davis)is similar. It contains no inactive ingredient except the gelatin capsule.

2. The indications for use, dosage, strength and labeling of the test product are identical to those of the reference product Humatin manufactured by Parke-Davis.

3. Paromomycin is a pre 62 drug which underwent DESI review and found to be effective against intestinal amebiasis. Therefore, a waiver for paromomycin can be granted based on 21 CFR 320.22 (c).

Recommendation

The Division of Bioequivalence agrees that the information submitted by Caraco Pharmaceutical on its Paramomycin Sulfate capsules, 250 mg falls under 21 CFR 320.22 (c) of the bioavailability/Bioequivalence regulations. The waiver of in vivo bioequivalence study for 250 mg capsules of Paramomycin Sulfate is granted.

AADA 64-171

JUN 27 1996

Caraco Pharmaceutical Laboratories, Ltd.
Attention: Annie Holt
1150 Elijah McCoy Drive
Detroit, MI 48202

Dear Madam:

This is in reference to your abbreviated new drug application submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Paromomycin Sulfate Capsules USP, 250 mg (base).

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research